

Contrast Media-Induced Nephropathy Following Diagnostic and Therapeutic Cardiac Catheterization

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It is estimated that 6,000 and 2,000 cardiac catheterization procedures per million inhabitants/year are performed in Western countries for diagnostic and therapeutic purposes. In order to perform these procedures, 1,800 tons of iodine are required all over the world to manufacture contrast media (CM). The number of procedures that require the use of contrast media (or dye) has increased over time, and the population submitted to it is growing older, presenting more comorbidities^{1, 2}.

Currently low-osmolar contrast media are used in approximately 75% of patients and the iso-osmolar contrast media, allegedly less toxic are becoming more popular¹. In spite of development of new contrast media, they still represent the third main cause of nosocomial-acquired acute renal failure (ARF) (10% of cases), substantially increasing hospitalization period, care costs and in-hospital morbi-mortality³⁻⁶.

The main goal is to address important aspects about the contrast-medium induced nephropathy (CMIN) that follows cardiac catheterization, including its definition, pathogenesis, incidence, risk factors, clinical picture, prevention, treatment and prognosis.

DEFINITION

To date, no consensus has been established regarding the definition of CMIN. The most used is the marked impairment of renal function related to a 25% increase in serum creatinine levels or an absolute increase of 0.5 mg/dL, 48 to 72 hours after the administration of contrast medium and in the absence of other causes. Some studies have used a 50% increase in serum creatinine level and 1 mg/dL to determine CMIN^{1,2,6-8}.

PATHOGENESIS

It is believed that the pathogenesis of CMIN is multifactorial. Vascular (hemodynamic) and tubular factors contribute to its development. However, the accurate pathophysiological mechanisms have not yet been clearly understood.

Vascular changes

One of the mechanisms involved in the contrast medium-induced acute renal failure (CMIARF) is the medium vasoconstrictive effect, which leads to medullar ischemia. Today, vasoconstriction is the subject of many studies^{8,9}. Actually, medium injection is followed by biphasic response – initial vasodilation that lasts only some seconds, but that increases renal blood flow, followed by variable periods of vasoconstriction and subsequent flow and glomerular filtration rate reduction^{10,11}.

The vasoconstrictive effect is stronger in the presence of nonsteroidal anti-inflammatory drugs (NSAIDs); however, the use of vasodilators such as dopamine and atrial natriuretic peptide can accentuate medullar ischemia due to redistribution of the blood flow from the medulla to the cortex¹⁰⁻¹³. Depletion of extracellular space in animals also enhances the more severe and persistent changes that can last up to 24 hours¹⁴.

Vasoconstriction seems to be related to changes in the renal intracapsular pressure, acute changes in renal perfusion secondary to initial vasodilation, direct effects of contrast media in smooth muscle contractility caused by changes in intracellular hydration, secondary effects of contrast media on smooth muscle contractility due to the release of vasoactive substances, changes in intracellular concentrations of calcium and aggregation of blood cells in the medullar flow^{8,10-13}.

Decreased renal blood flow may be a consequence of the osmolarity of contrast media¹⁵. It has been shown that intrarenal pressure and blood flow are inversely related, i.e., when intrarenal pressure increases, blood flow diminishes and vice versa¹⁶. Therefore it seems that decreased blood flow and glomerular filtration rate can be explained by increased intratubular hydrostatic pressure induced by hyper-osmolar contrast media^{1,8}. This phenomenon is supported by important reduction of these effects when low-osmolar contrast media are used⁸.

Direct effect of contrast media osmolarity on vascular

smooth muscle cells resulting in vasoconstriction is another possible component of hemodynamic changes^{8,10-13}. Calcium may be another mediator of this phenomenon because it has been demonstrated that some of its antagonists reduce vasoconstriction associated with administration of contrast media¹⁷.

Adenosine is a vasodilator that acts on peripheral circulation; however it promotes vasoconstriction at the renal cortex¹⁸. Studies carried out in dogs have shown that adenosine antagonist, theophiline, and its agonist, dipiridamol weaken and accentuate, respectively, the contrast medium-induced vasoconstrictive effect¹⁹. However, further research is necessary to better understand the role played by adenosine.

Peptides such as endothelin, angiotensin II, vasopressin, atrial natriuretic peptide and bradikinin play important roles in renal physiology. Endothelin, a powerful vasoconstrictive agent, reduces the blood flow and the glomerular filtration rate²⁰. Many studies suggest that endothelin may play an important role in CM-induced hemodynamic changes, which would stimulate its release by endothelial cells, increasing its plasma and urinary levels. In contrast to the importance of endothelin as a mediator in the decrease of renal blood flow caused by CM is its prevailing action on the efferent arteriole such as angiotensin II, which is classically considered to increase filtration fraction. This is not consistent with the previously described effects¹⁵. To sum up, new studies should be performed to confirm the role played by endothelin in CM-mediated vascular changes.

It is unclear if angiotensin is a vasoconstriction mediator. Studies with angiotensin II blockers or its receptors for and against this hypothesis are being carried out. Controlled studies with human beings are necessary to definitely evaluate the role played by this peptide in the pathogenesis of CM-induced ACF.

Changes caused by contrast media on vasodilator substances also contribute to the occurrence of ARF. Nitric oxide synthesis reduction at the renal cortex after CM administration is well-known²⁷. Additionally, pharmacological inhibition of vasodilator prostaglandin and nitric oxide increase MC nephrotoxicity^{13,28}. Endothelium dysfunction caused by diabetes, hypertension and atherosclerotic disease, with subsequent reduction of vasodilator release may explain the increased risk of CM-induced ARF presented by these patients².

It has been suggested that CM-induced vasoconstriction could be caused by a tubuloglomerular feedback mechanism, triggered by the macula densa when in contact with hypertonic solutions. Angiotensin II, adenosine and calcium would participate as intermediate mediators promoting vasoconstriction of the afferent arteriole causing the reduction of glomerular filtration rate and the increase of the renal vascular resistance. There is increasing evidence that adenosine is the main mediator of the tubuloglomerular feedback⁸.

Tubular changes

Possible direct toxic effects of CM on tubular function has been less studied recently, but they include: direct cellular injury, tubular obstruction and osmotic changes⁸.

It has been shown that contrast media reduce the secreting function of the proximal tubules of cortical nephrons, suggesting an independent toxic effect caused by hemodynamic changes²⁹. There is evidence of direct cellular injury, shown by changes in the energy metabolism of cells in the proximal tubules, release of intracellular enzymes and CM-produced histological changes³⁰. Among them, it is worth highlighting the proximal renal tubule vacuolization (osmotic nephrosis) which is probably caused by increase of giant lysosomes. This is enhanced by using iso-osmolar CM, is completely reversible and is not necessarily related to the progress to ARF^{1,8,31}.

Studies that have evaluated patients with multiple myeloma and who developed CM-induced ARF describe massive deposition of Bence-Jones protein, causing tubular obstruction. At first it was thought that this mechanism was responsible for the particularly high risk presented by these patients^{32,33}. However, it is unlikely that this deposition will take place with the new contrast media and affect well-hydrated patients. Furthermore, the importance of the deposition of the Tamm-Horsfall protein and uric acid crystals in CMIN has not been proved^{34,35}.

Arguments used to defend possible tubular obstruction as the primary cause of CMIARF include the observation that nephrograms are usually dense immediately after the procedure and both kidneys are enlarged, simulating acute ureteral obstruction. Maintenance of this picture for a long period of time could result in a sustained reduction of the renal blood flow⁸. However, there is no pathological evidence to prove that this mechanism is the main etiological agent of CMIN^{2,11}.

Important but transient proteinuria affect animals and human beings following angiography with hypertonic agents^{35,36}. However, whether this transient increase in the permeability of the glomerular basal membrane plays an important role in promoting CMIN or not is unclear. Urinary excretion of many tubular enzymes as indication of these cells' injury has also drawn much interest, but specificity both of enzimuria and proteinuria is debated^{2,8,37,38}. Therefore it seems that there are no advantages in monitoring these urinary abnormalities in patients that undergo dye-based tests².

Unfortunately, it is difficult to totally dissociate the true effects of direct tubular injury from the secondary effects of renal ischemia, which can cause cellular damage due to lipid peroxidation, associated with increased production and reduced removal of oxygen free radicals⁹. The importance of oxygen reactive species as

factors related to the pathogenesis of the CMIN has been shown in experimental studies^{8,9,14,39}. Administration of catalase¹⁴ or dismutase superoxide³⁸ or deferoxamine iron chelation⁴⁰ can improve the CM-induced hemodynamic and functional changes.

To sum up, evidences favor medullar ischemia as the central pathophysiological factor of CMIARF. The role of possible mediators involved in this process is still unclear. Medullar ischemia may be caused by the unbalance between vasoconstrictive and vasodilator factors, independently acting on the renal cortex and medulla. Therefore, changes in the metabolism of prostaglandins, nitric oxide, endothelin, adenosine or other substances can contribute to it. Actually the pathophysiological mechanisms of CMIN are not necessarily the same in all patients. In addition to that, patients with endothelial cell dysfunction, such as individuals with diabetes, hypertension or atherosclerotic disease may be more sensitive to developing ACF following dye-based tests².

INCIDENCE

Incidence of CMIN varies substantially among several studies, depending on the diagnostic criteria used and individual risk factors presented by the patients^{1,9}. It is estimated that it affects 1% to 6%^{41,42} of individuals in non-selected groups, but it may affect up to 40% to 90%^{12,43-46} of high risk patients, especially those with chronic renal failure (CRF) and diabetes mellitus (DM). The incidence of CMIARF also varies depending on the definition used: 2.0% (1.0 mg/dL increase in serum creatinine)⁴⁷; 3.3% (0.5 mg/dL increase in serum creatinine)⁴⁸; and 14.5% (25% increase in serum creatinine)⁴⁹.

RISK FACTORS

A study with 1,077 individuals submitted to cardiac catheterization with nonionic contrast agent revealed that although 73% of them presented a discreet transient increase of serum creatinine, this had no clinical impact in most cases⁴¹.

However, groups with higher likelihood of developing ARF following dye-based exams have been determined as well as possible risk factors such as pre-existing ARF, DM, volume of CM administered, dehydration, atherosclerotic disease, congestive heart failure^{1,9}, nephritic syndrome, liver cirrhosis, concurrent use of nephrotoxic drugs, use of high-osmolar CM¹, age, male gender, multiple myeloma⁹, hypoalbuminemia and hyponatremia⁴⁵. Other risk factors for CMIN are suggested following coronary interventions: systemic arterial hypertension, emergency procedures, intra-aortic balloon⁴⁷; onset of acute myocardial infarction 24 hours before the procedure, unsuccessful procedure; interventions on the left coronary artery; presence of coronary, peripheral and systemic vascular complications related to the procedure⁴⁸. It is key to identify patients that present any of these risk factors in order to implement

severe prophylactic measures.

Chronic renal failure (CRF)

The majority of most recent studies confirmed that CRF is the most important risk factor of CMIN, followed by DM^{2,41,43-51}. Results of all studies that compared patients with and without CRF have pointed that the first group was more likely to develop CMIN^{41,44-46,48, 52}.

Prospective studies involving approximately 9,000 patients that underwent cardiac catheterization presented an exponential increase in their risk to develop ARF when serum creatinine before the procedure was above 1.2 mg/dL, attaining a 30.6% index in patients with basal creatinine above 3.0 mg/dL. Subjects with serum creatinine higher than 1.5 mg/dL had a 21-fold increase in their risk of developing CMIARF compared to those whose renal function is normal^{41,48,50}.

According to a study carried out by Bartholomew et al⁴⁷ with 20,479 patients that had undergone coronary interventions, the incidence of ARF following the procedure is inversely proportional to the creatinine clearance: higher or equal to 90 mL/min: 0.6%; between 60 to 89 mL/min: 1.4%, and lower than 60 mL/min: 6.4%. Manske et al studied a group of 59 insulin-dependent diabetic patients with a mean creatinine clearance of 14 mL/min who have undergone coronary angiography. Out of those patients, 50% presented recurrence of renal failure. Ten patients had to be submitted to dialysis during the follow-up, and 7 of them in the first six days following the procedure⁴³.

Diabetes mellitus (DM)

Most studies confirmed that the risk of developing MCIARF is similar in diabetic individuals without CRF and in non-diabetic subjects^{41,46,50,52}. On the other hand, almost every study has evidenced a strong association between DM with pre-existing renal dysfunction and CMIARF^{12,44,46,49-51}. McCullough et al⁴⁹ examined 1,826 consecutive patients submitted to coronary intervention. In their study, 14.5% of patients developed CMIN and 0.77% had to undergo dialysis. This latter procedure was required by 43% of diabetic patients with creatinine clearance below or equal to 20 mL/min, but by no patient whose clearance was above 47 mL/min.

Rudnick et al⁵⁰ performed a study with 1,196 patients that underwent cardiac catheterization. The incidence of MCIN observed by them was DM and normal renal function: 0.6%; isolated CRF: 6%; DM and CRF: 19.7%. Results obtained by Barret et al⁵¹ with 249 patients supported those findings; the incidence of MCIN in their series was: non-diabetic patient with serum creatinine level lower than 2.25 mg/dL: 6%; diabetic patient with serum creatinine level lower than 2.25 mg/dL: 11%; non-diabetic patient with serum creatinine above 2.25 mg/dL: 16.7%; and diabetic patient with serum creatinine above 2.25 mg/dL: 33.3%.

In conclusion, although diabetic patients with normal renal function require special care, their risk to develop CMIARF is low. However, diabetic individuals with CRF represent a group whose risk is extremely high and therefore, prophylactic measures should be always adopted.

Volume of contrast media (CM)

Several studies pointed a correlation between the volume of contrast media administered and risk to develop ARF^{43,44,45,49,50,52-54}. Out of the 1,826 patients submitted to percutaneous coronary interventions examined by McCullough et al⁴⁹, 14 individuals had to undergo dialysis. The volume of MC administered to each of them had been always equal or higher than 100 mL. However, other studies have shown that even smaller volumes of CM may induce renal failure and consequently dialysis^{43,55}. Manske et al⁴³ found that 26% of the insulin-dependent diabetic patients with advanced chronic renal failure studied had a recurrence episode when less than 30 mL of CM was injected during cardiac catheterization. When the dose was above 30 mL, this rate went up to 79%. For each extra 5 mL of CM, the risk for ARF increased 65%.

Cigarroa et al⁵⁴ classified patients with serum creatinine level above 1.8 mg/dL in two groups: the first without any limits regarding the volume of CM administered and the second with restricted volume, according to the individual's weight and serum levels of creatinine. The incidence of ARF in both groups was 26% and 2%, respectively. All patients that developed CMIN were diabetic.

In light of these findings, the lowest possible volume of CM is recommended, as well as the ruling out of routine ventriculography in high-risk patients.

Contrast media osmolarity

Similar results comparing different osmolar contrast media and nephrotoxicity were found in relevant studies. The meta-analysis carried out by Barret and Carlisle⁵⁶ showed that out of the 31 controlled, randomized studies totaling 5,146 patients 22 favored the low osmolar CM. But the authors observed a statistically significant reduction in CMIN incidence when low osmolar CM was administered only when serum creatinine level was above 1.35 mg/dL or when glomerular filtration rate was lower than 70 mL/min before contrast was administered.

Rudnick et al⁵⁰ have examined 1,196 individuals and found no difference between low and high osmolar CM and nephrotoxicity (iohexol and diatrizoate, respectively) in patients with normal renal function, which reflects the low risk presented by these individuals. For higher risk patients, the incidence of CMIN was significantly lower when low-osmolar CM was used: 12.2% vs. 27% in individuals with CRF and 33.3% vs. 47.7% in diabetic

individuals with CRF.

A multicentric study with 1,194 patients who had undergone scheduled coronary angiography compared diatrizoate (high osmolar CM) and iohexol (low osmolar CM). CMIN affected 27% (diatrizoate) and 12% (iodexol) of individuals that presented both CRF and DM⁵⁷.

Contrary to previous evidence, data from three studies^{51,58,59} with 657 patients whose serum creatinine level was above 1.35 mg/dL pointed out a less important benefit of low osmolar contrast media in individuals with impaired renal function and discussed its cost-effectiveness. However, less than 20% of the cases evaluated presented severe renal impairment (serum creatinine level above 2.25 mg/dL).

Other studies also failed to support an indisputable advantage of low osmolar CM. A prospective randomized study of 443 patients that underwent cardiac catheterization receiving either iopamidol (low osmolar) or diatrizoate (high osmolar) carried out by Schwab et al⁶⁰ revealed a non-significant difference of CMIN between the two groups. Serum creatinine level increase of at least 0.5 mg/dL was observed in 10.2% of subjects that had been given diatrizoate vs. 8.2% among those that had received iopamidol. As for 160 individuals considered high risk patients because they had DM, congestive heart failure and/or CRF, 17% of those that had received high osmolar CM vs. 15% of those that had received low osmolar CM developed CMIN. Only 5% of this sample had serum creatinine higher than 3 mg/dL.

Two meta-analyses studies examined 18 and 14 studies comparing iso-osmolar to low-osmolar CM. No significant difference was found regarding ARF^{61,62}. A prospective, randomized study with 856 low risk individuals who underwent coronary intervention with administration of iodixanol (iso-osmolar CM) or ioxaglate (low-osmolar CM) did not reveal any difference regarding the incidence of CMIN, although the study did show an expressive 45% reduction in important in-hospital adverse events⁶³.

A multicentric study published by Aspelin et al⁶⁴ evaluated the effect of coronary or aortofemoral angiographic studies on 129 diabetic patients with serum creatinine level between 1.5 and 3.5 mg/dL, but results did not support the findings above mentioned. The incidence of renal failure recurrence in patients with chronic renal failure was 3.0% when iodixanol, an iso-osmolar contrast medium was used, compared to 26% when iohexol (low-osmolar CM) was administered. Another study evaluated the same media in a total of 124 individuals with serum creatinine above 1.7 mg/dL. It also showed that iodixanol was less nephrotoxic than iohexol with CMIN incidence of 3.7 and 10%, respectively⁶⁵.

Further studies are necessary, especially with high risk patients for comparing contrast media with different osmolarity. Low-osmolar CM should be used in the presence of CRF or of CRF plus DM. Considering that low

osmolar CMs cost three to five-fold more than high osmolar CMs⁹, the regular use of low-osmolar CMs in patients with normal renal function is not justified. Evidence about iso-osmolar contrast media is controversial.

Other risk factors

Dehydration is a known risk factor for CMIN⁶⁶. However, most recent studies have found it difficult to consider dehydration as an independent variable due to the strict hydration protocols used⁹.

Concurrent administration of CM and nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs and aminoglycosides, and possible acute prescription of angiotensin-converting enzyme inhibitors should be avoided. Patients with diabetic nephropathy that undergo therapy with drugs to reduce proteinuria, but that present normal blood pressure may not need to discontinue their use before a contrast-based test¹.

Multiple myeloma has been traditionally considered an independent risk factor for CMIARF³³. A study review totaling 476 subjects with this condition failed to confirm that⁶⁷. It is possible that high risk is related to an underlying renal failure and/or volume depletion, resulting in increased intratubular deposition of filtered light chains^{66,67}.

Congestive heart failure has been considered an independent risk factor for CMIN by some studies^{45,53,68,69}; however, this was not supported by others^{41,70}. Many subjects of those studies were receiving diuretics before cardiac catheterization or were not adequately hydrated due to the fear that it could trigger an acute pulmonary edema after the procedure. Therefore, depletion of extracellular space and activation of renal vasoconstrictive mechanisms could be related to triggering CMIARF and consequently the results mentioned².

Some studies have found that older age is associated with an increased risk for CMIN^{4,71} and that elderly patients submitted to cardiac catheterization are more likely to develop further general complications^{72,73}. However, Rich et al⁴⁵ conducted a prospective study and examined the incidence and clinical course of CMIARF in 183 individuals whose age was at least 70 years and who have had been submitted to cardiac catheterization – results of this study were similar for older and younger patients. As older subjects are more likely to present risk factors for CMIN, such as CRF, DM and depletion, risk may be really higher in this population; however, older age as an isolated variable should not be considered a counter-indication for exams that require contrast media⁴⁵.

Other risk factors, such as atherosclerotic disease⁴¹ and male gender⁴⁴ have not been considered independent risk factors in more recent research.

CLINICAL FINDINGS

Medium-contrast induced acute renal failure is

asymptomatic, non-oliguric and reversible in most patients. Serum creatinine usually increases 24 to 72 hours after the patient has been exposed to the medium contrast and reaches its peak in 3 to 5 days (usually a 0.5 – 3.0 mg/dL increase), and is lowered to its initial level in 7-14 days^{8,9,74,75}.

A more severe form of ARF due to CMIN can be also observed, especially in high risk patients. In this case, oliguria is observed 24 hours following the administration of the CM, and serum creatinine level is usually above 5 mg/dL^{8,9}. Oliguria is transient in most cases, and is usually present for 2 – 5 days. Serum creatinine peak is observed within 5 – 10 days and lowers to its initial value 14 – 21 days later⁸.

Urinalysis usually shows a pattern of acute tubular necrosis. It may also show tubular epithelial cells and coarse granular cylinders⁹, but the urinary sediment may be non-specific with minimal proteinuria². Some studies pointed that the fractional excretion of sodium is low, but this has not been confirmed by others⁶⁶. Low urinary sodium concentration and extremely low fractional excretion of sodium may be present in severe CMIARF during the oliguric stage⁷⁴. However, changes in urinary standards such as fractional excretion of sodium, transient proteinuria and enzimuria have not proved to be useful to confirm the diagnosis of CMIN^{38,74,75}.

It is important to mention that patients with atherosclerotic disease who underwent angiography also present high risk for developing secondary ARF due to an atheroembolic event⁷⁶. Differently from CMIN, renal atheroembolic disease causes late ARF (7 days to weeks following the contrast-based test). It is often associated with short periods of eosinophilia, hypocomplementemia and other evidence of atheromatous emboli event, such as livedo reticularis, ischemia or gastrointestinal infarction. The clinical picture of ARF caused by atheromatous embolism lasts longer and is often associated with minimal recovery of the renal function⁹.

PREVENTION

In contrast to most of the other forms of nosocomial-acquired ARF, CMIN can be prevented. Several prophylactic measures have been proposed based on better understanding about the pathogenesis of this condition.

No other remarks related to volume and osmolality of contrast media, previously discussed, will be added.

Acetylcysteine

In addition to being an antioxidant, acetylcysteine has vasodilator properties. It increases the expression of the nitric oxide synthase^{77,78} and could prevent CMIN both by reducing the direct oxidative damage and by improving the kidney hemodynamic status.

From 2002 to 2005, four meta-analysis studies have

presented results favorable to the use of acetylcysteine to prevent CMIARF⁸⁵⁻⁸⁸, although some studies have failed to prove its efficacy⁷⁹⁻⁸⁴.

Out of the studies that have not presented favorable results, the Brazilian multicentric study recently published by Gomes et al⁸⁴ stands out. The sample consisted of 156 subjects submitted to cardiac catheterization or coronary intervention in which only low-osmolar CM was used – no difference was found regarding CMIN incidence between the group that received the drug and the placebo group.

A meta-analysis conducted by Alonso et al⁸⁵ examined eight randomized controlled studies with 885 patients whose serum creatinine level was equal to or above 1.2 mg/dL or whose creatinine clearance was lower than 70 mL/min. acetylcysteine reduced the risk for CMIN.

Five prospective, randomized studies were examined by another meta-analysis research, which revealed a 20% reduction of CMIN in the group of patients that had received prophylactic treatment with acetylcysteine as compared to the placebo group⁸⁶.

Birck et al⁸⁷ and Isenbarger et al⁸⁸ analyzed the same seven randomized studies comparing acetylcysteine and hydration, with the latter as a single variable in 805 subjects with CRF and confirmed the efficacy of this drug. Birck et al observed a 56% reduction in the relative risk of renal failure recurrence in patients with CRF when this medication was used as preventive therapy. The second group of researchers concluded that for each 9 patients treated with acetylcysteine, one case of CMIN is prevented.

The dose used in most of the studies included in the above mentioned meta-analyses was 600 mg twice a day, from the day before the dye was administered. Briguori et al⁸⁹ compared this to a higher dose (1,200 mg twice a day, or twice as much) in a sample of 224 patients whose serum creatinine was equal to or above 1.5 mg/dL or whose creatinine clearance was lower than 60 mL/min. CMIN frequency was lower in the group of patients that had received the higher dose (3.5% vs. 11%), but this difference was significant only when the volume of dye used was equal to or higher than 140 mL.

At emergency situations, endovenous administration has been proposed since there is not enough time for oral administration of acetylcysteine. Webb et al⁸¹ distributed 487 subjects in two groups: hydration and hydration associated with a single dose of 500 mg IV of acetylcysteine immediately before the administration of the dye. Early discontinuation of the study was recommended owing to lack of effectiveness of the drug. In contrast, another study presented favorable results, although the sample consisted of only 80 individuals submitted to hydration or to the IV administration of acetylcysteine – 150 mg/kg, 30 minutes immediately before and 50 mg/kg following the procedure using the dye. CMIN affected 21% and 5% of the population,

respectively⁹⁰. It is important to highlight the highest dose and the use of the drug before and after injection of contrast medium.

Ochoa et al⁹¹ evaluated the oral administration of acetylcysteine in high doses (1,000 mg one hour before and four hours following coronary angiography and/or coronary intervention) in 80 patients with CRF. Their results pointed to an 8% incidence of CMIN in the group that received the drug vs. 25% in the placebo group, suggesting that the proposed prophylactic regimen is effective.

Although some studies debated the effectiveness of acetylcysteine, the benefit of the prophylactic use of acetylcysteine to prevent CMIN was confirmed by the meta-analysis studies mentioned. Furthermore, characteristics such as low cost, high availability, oral administration and limited adverse effects favor its use for this purpose. Several dose regimens were used however, the most studied was 600 mg twice a day, for two days, starting on the day before the procedure.

Ascorbic acid

Ascorbic acid has antioxidant properties and has been used as a nutritional supplement. A randomized, placebo-controlled study evaluated its efficacy to prevent CMIN. This study evaluated 231 patients whose serum creatinine was equal to or higher than 1.2 mg/dL and who had undergone coronary angiography and/or coronary interventions. The dose of vitamin C used was 3 g, at least two hours before the contrast medium was injected plus 2 g at night and in the morning following the procedure. Recurrence of renal failure in CRF patients affected 9% and 20%, respectively, of the sample that received ascorbic acid and the placebo group. Such results suggest that vitamin C is effective to prevent CMIN, in addition to being safe, well-tolerated, inexpensive and widely available; however, further studies are required with a larger number of patients to confirm this hypothesis⁹².

Adenosine antagonists

A possible protective role of theophylline and aminophylline against contrast medium-induced nephrotoxicity was studied. Some research have suggested theophylline's efficacy^{93,94}, but this has not been confirmed by some other studies^{95,96}; therefore larger prospective studies are necessary to define the importance of adenosine antagonists in this context.

Endothelin antagonists

There are two receptors for endothelin: ETA e ETB. Experimental studies with rats have shown that they played different roles: ETA receptor is vasoconstrictive and is found in the smooth muscle whereas ETB receptor promotes vasodilation via the release of nitric oxide and prostacyclin and is found in endothelial cells⁹⁷. However,

both subtypes are involved in endothelin's vasoconstrictive action in human blood vessels⁹⁸.

Experimental studies have pointed that a selective antagonist of the ETA receptors prevented creatinine increase after the administration of contrast medium⁹⁹; however blockage of ETB receptors did not promote any renal protection¹⁰⁰.

Wang et al¹⁰¹ conducted a randomized, placebo-controlled study to evaluate the effectiveness of a mixed ETA/ETB receptor antagonist, (SB290670), to prevent MCIN. The sample comprised 158 individuals whose serum creatinine level was equal to or above 2.0 mg/dL and who had undergone cardiac catheterization. Recurrence of renal failure in patients with CRF was higher in patients that received the drug vs. the placebo group (56% vs. 26%), determining its harmful effect.

It is clear, then, that further studies are required to determine if specific antagonists of endothelin receptors are useful in the preventive management of CMIN.

Calcium channel antagonists (or Blockers)

Few prospective studies have shown that the calcium channel antagonists have attenuated the glomerular filtration rate reduction following exposure to a contrast medium^{102,103}. However, other studies did not prove a reduced incidence rate of CMIN with prophylactic use of these drugs^{104,105}. Because of the small number of clinical trials, all of them with a reduced number of patients and controversial results, an in-depth study with a large number of subjects is required to adequately evaluate the efficacy of calcium channel blockers to prevent CMIN in high risk patients.

Arginine

Arginine is the substrate for the nitric oxide production. The effectiveness of the IV administration of 300 mg/kg of arginine during coronary angiography was evaluated by a randomized, placebo-controlled study to prevent CMIN in patients with CRF. No benefit has been observed¹⁰⁶.

Sodium bicarbonate

Recent results from a prospective, randomized study with a total of 119 individuals whose serum creatinine was equal to or above 1.1 mg/dL were published. It compared the use of sodium bicarbonate and sodium chloride, both at a concentration level of 154 mEq/L, as a prophylactic hydration procedure following exposure to contrast medium. Eight patients out of the group that had received sodium chloride developed CMIN (13.6%) compared to only one (1.7%) from the sodium bicarbonate group. Although further studies with larger samples are necessary to confirm these results, the infusion of sodium bicarbonate represents a safe, practical, inexpensive and simple method to prevent ARF induced by contrast media¹⁰⁷.

Diuretics

Manitol and furosemide were compared to saline solution to prevent CMIN. Results were not effective; on the contrary, it is possible that they might be harmful^{12,108,109}.

Stevens et al¹¹⁰ have shown that forced diuresis, induced by the administration of furosemide, manitol and low dose of dopamine associated with the attempt to maintain the intravascular volume with IV crystalloid solution promoted mild protection against CMIN. This finding was more evident in the group of patients whose mean urinary flow was above 150 mL/h.

Based on that, the routine use of manitol and furosemide as prophylactic agents is not recommended. It should be mentioned that both substances may deplete the extracellular space therefore increasing nephrotoxicity risk promoted by contrast media.

Dopamine

Dopamine stimulates two types of receptors DA1 and DA2 in a non-selective manner, in addition to act on alpha and beta adrenergic receptors when administered in high doses. Activation of DA1 receptors increases renal blood flow and natriuresis in contrast to stimulation of DA2 and adrenergic receptors, associated with vasoconstriction⁹.

Several researchers have studied dopamine's efficacy to prevent CMIN. Weisberg et al¹² confirmed increased renal blood flow; however, their results have shown a higher incidence of recurrence in diabetic patients treated with this drug. Some other studies did not prove any advantage when dopamine was used compared to hydration as a prophylactic measure against CMIN^{95,111}. Abizaid et al⁹⁵ have described some harmful effects when dopamine is used to treat established ARF, caused by contrast medium.

In contrast to findings of those researchers, two prospective trials have shown that dopamine, administered at a dose of 2.5 – 3.0 µg/kg/min, 12 to 24 hours following CM exposure, prevented nephrotoxicity from affecting individuals with mild renal dysfunction^{112,113}. But results from these studies are limited because of the small number of patients and short follow-up.

In the light of controversial evidence, routine use of dopamine with intention to avoid CMIN is not recommended.

Fenoldopan

Fenoldopan is a selective dopamine-1 receptor agonist. It has been approved to manage hypertensive emergencies via intravenous administration. It has a powerful vasodilator action both systemic and on the renal arterioles, but it does not stimulate adrenergic and DA2

receptors even when high doses are given¹¹⁴.

Some randomized, placebo-controlled studies to evaluate the prophylactic effect of this drug against CMIN have been published. Tumlin et. al.¹¹⁵ conducted a trial with 45 patients whose serum creatinine level was equal to or higher than 2.0 mg/dL. They compared a dose of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ of fenoldopam to hydration as a single variable. Incidence of renal failure recurrence in patients with CRF was 21% in the fenoldopam group and 41% in the group that received only saline solution.

Kini et al¹¹⁶ compared the frequency of CMIN following coronary intervention in 150 patients that had received fenoldopam with another 150 in the control group. Results were 4.7% and 18.8%, respectively.

Contrary to the previous results presented, a multicentric study has failed to prove the efficacy of fenoldopam to prevent CMIN. A sample of 315 individuals with creatinine clearance lower than 60 mL/min were randomly selected to receive either the drug, at a dose of up to 0.1 $\mu\text{g}/\text{kg}/\text{min}$ or placebo¹¹⁷.

The comparison between fenoldopam and acetylcysteine was also controversial. Briguori et al¹¹⁸ studied 192 patients with CRF who were randomly assigned to two groups: acetylcysteine: 1,200 mg, twice a day, and fenoldopam: 0.1 $\mu\text{g}/\text{kg}/\text{min}$; both related to hydration. Efficacy of acetylcysteine was higher, with incidence of CMIN of 4.1% vs. 13.7%. Another study examined 123 individuals with CRF and the results were unfavorable to acetylcysteine and to fenoldopam when compared to hydration. Recurrence rates were 17.7%, 15.7% and 15.3%, respectively¹¹⁹.

Because of the controversial results that have been found to date, further studies are necessary to provide a final evaluation of the efficacy of fenoldopam to prevent CMIN.

Hemodialysis

Prophylactic hemodialysis was considered to prevent further impairment of the renal function in high risk patients when performed immediately following the dye administration. Several studies have proved that this strategy significantly reduces the plasma levels of contrast medium; however, it does not affect the frequency of Acute Renal Failure¹²⁰⁻¹²⁴.

Marenzi et al have evaluated the effectiveness of hemofiltration, a therapeutical procedure to provide continuous renal replacement to prevent CMIN. They examined 114 individuals with serum creatinine above 2.0 mg/dL that had undergone coronary intervention. In the hemofiltration group, renal functional became poorer only for 5% of participants; whereas this happened in 50% of those in the control group. In-hospital mortality rate and within a year also indicated better results for hemofiltration: 2% vs. 14% and 10% vs. 30%. It is important to emphasize that hemofiltration is an invasive

procedure with high costs. Its cost-effectiveness has not been determined yet, but it can be suitable for high risk patients.

Hydration

Over the last decades, most large studies about CM nephrotoxicity have incorporated hydration protocols, confirming the recommendation that all patients should be hydrated, either orally or via IV, although there are no clinical trials directly comparing its use. This strategy should be introduced intravenously before and maintained after the administration of the potential nephrotoxic agent, especially for patients at high risk of developing CMIN.

The clinical goal is to maintain a positive fluid balance, with high urinary output. The ideal regimen has not been determined yet; however, many have been used, with infusion rates varying from 100 to 150 mL/h or 1.0 to 1.5 mL/kg/h, aiming to produce urinary volumes of 75 to 125 mL/h^{12,41,46,60,108}. Close monitoring of total fluid balance is key to adjust hydration as necessary.

A prospective, randomized study with 1,620 patients who had undergone coronary angioplasty was performed by Mueller et al¹²⁵, who evaluated two hydration regimens: isotonic and hypotonic saline solution (sodium chloride: 0.45% and glucose 5%). Liquids were offered in the morning of the scheduled procedure or immediately before it in emergency cases. CMIN was significantly lower in the group that received isotonic saline solution (0.7% against 2.0%). Three pre-defined subgroups have benefited from receiving isotonic hydration: women, diabetic patients and those who received 250 mL or more of contrast medium.

Atrial natriuretic peptide

The possible protecting effect of this peptide in CMIN was examined in by a prospective study with 247 patients with CRF who were randomly assigned to receive three different doses of this substance or placebo. None of the three doses evaluated proved its protective role against contrast medium nephrotoxicity, even among diabetic patients¹²⁷. Therefore, there is no evidence to support the use of atrial natriuretic peptide as prophylactic agent against CMIN.

Prostaglandins

A double-blind, randomized study evaluated the prophylactic use of prostaglandin E1 (PGE1) in 117 patients with serum creatinine level equal to or above 1.5 mg/dL who had undergone several tests that required administration of contrast medium. Doses of 10, 20 and 40 ng/kg/min of IV PGE1 administered one hour before the procedure for six hours. The 20 ng/kg/min dose presented better and statistically significant results compared to all the other groups to prevent CMIN¹²⁸. However, further studies are required to confirm these results.

The Hemodynamics and Interventional Cardiology services of the two hospitals that participated in this review seek to use the least possible amount of contrast medium, to discontinue the concurrent use of nephrotoxic drugs and to stratify the risk of developing CMIN in all patients that are going to be submitted to cardiac catheterization, either for diagnosis and/or therapeutical purposes. Oral hydration is encouraged to patients with low risk of developing CMIARF. The procedure for high risk patients involves intravenous hydration with an isotonic saline solution, at the dose of 1,000 mL, 12 hours before and 12 hours following exposure to the dye, with close monitoring of fluid balance in addition to administration of acetylcysteine, 600 mg orally every 12 hours, for two days, starting 24 hours before catheterization. Less volume of isotonic saline solution, based on clinical parameters, is given to patients who cannot bear such a hydration program.

TREATMENT

Established treatment of CMIN encompasses conservative measures and dialysis in accordance to the severity of renal dysfunction and the resulting complications⁸.

Conservative management involves daily monitoring of the patient's weight, with close assessment of fluid balance, infusion of saline solution and periodical measurement of serum electrolytes, such as creatinine and urea. Protein intake should be limited to approximately 0.5 g/kg/day.

Out of the patients who developed ARF after being exposed to contrast medium, 0.44% to 25% of them may need to undergo dialysis in the subgroups at high risk^{5,49,68,129-132}. Dialysis is indicated in the presence of severe hyperkalemia, metabolic acidosis or volume overload that do not respond to conservative measures. Signs and symptoms of uremia also indicate dialysis. Recovery may be hard due to increased diuresis and resulting extracellular depletion and electrolyte loss, which require early detection and adequate corrective measures⁸.

PROGNOSIS

Contrast-medium induced nephrotoxicity increases hospitalization period and in-hospital morbidity and mortality in the medium and long run⁴⁸.

In-hospital mortality of patients with CMIN varies from 7.1%, in non-emergency situations, up to 66%, in high risk patients with acute myocardial infarction and chronic renal failure^{5,48,49,133}. In one year, it can attain levels of 12.1% to 27.7%^{48,68,134}. In-hospital mortality rate of patients that require dialysis owing to CMIARF varies from 22.6% to 39%^{49,68,130}, and may affect 45.2%

in one year⁶⁸.

Levy et al⁵ evaluated 16,248 patients who underwent procedures that required administration of contrast medium. Mortality rate in individuals with and without CMIARF was 34% and 7%, respectively. Events that contributed to higher levels of morbidity and mortality of patients with renal dysfunction were sepsis, bleeding, coma and respiratory failure.

A prospective study by Freeman et al examined 16,592 coronary interventions. The study revealed a 0.44% incidence of CMIN that required dialysis. The in-hospital mortality rate in this group of patients was 39% but only 1.4% of the subjects that did not present this complication died. Another study with 20,479 patients who had been submitted to coronary angioplasty has demonstrated that patients that had developed ACF following the procedure had a 15-fold increased chance of longer hospitalization (over four days) and were more likely to present major cardiac events (death, acute myocardial infarction and re-occlusion of the vessel submitted to angioplasty)⁴⁷.

A retrospective trial by Rihal et al⁴⁸ with 7,586 consecutive patients submitted to coronary intervention have shown that 22% of the subjects who developed ARF after the procedure died during hospitalization compared to only 1.4% among those others whose renal function had not worsened. Mortality rates at 1 and 5 years of CMIN survivors were respectively 12.1% and 44.6%, much higher than 3.7% and 14.5% observed in patients without acute renal failure.

After having evaluated 1,826 consecutive patients submitted to coronary intervention, McCullough et al⁴⁹ found an incidence rate of 14.5% for CMIN and of 0.77% for dialysis-required CMIN. In-hospital mortality rates among patients without ARF, with ARF and among those with ARF that required dialysis were 1.1%, 7.1% and 35.7%.

Gruberg et al⁶⁸ have retrospectively studied the prognostic implications of renal failure recurrence after the administration of contrast media in 439 patients whose serum creatinine level was equal to or above 1.8 mg/dL and that had undergone coronary interventions. Out of the 161 (37%) individuals who developed CMIN, 19% required dialysis and 14.9% died during hospitalization compared to only 4.9% of those whose renal function had not worsened. Within a year, mortality rate attained 45.2% in patients that needed to undergo dialysis, 35.4% in those that did not require that procedure and in 19.4% of individuals whose serum creatinine profile had not worsened.

The impact of pre-existing renal failure and subsequent development of CMIN in 2,082 patients submitted to primary coronary angioplasty to treat acute myocardial infarction was assessed by Sadeghi et al¹³⁴. Mortality

rates at 30 days (16.2% vs.1.2%) and at one year (23.3% vs. 3.2%) were significantly higher in individuals that developed acute renal failure after coronary intervention.

To conclude, knowledge about CMIN has significantly increased, but there are still many questions to be clarified, regarding many aspects, from its pathogenesis to therapy, not to mention the consistent high morbidity and

mortality rates. Further detailed studies are required in order to implement a more effective prophylactic measure and to improve its treatment.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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